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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FULBRIGHT & JAWORSKI, LLP
666 FIFTH AVE
NEW YORK, NY 10103-3198

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/023,182	STOCKERT ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-37,40 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-37,40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of group II, Claims 32-37 in Paper of 01/30/04 is acknowledged and entered.

Applicant adds new claims 40-41, which are related to claims 32-37.

Applicant asserts that point 1 of the restriction requirement is not understood.

It is noted that point 1 of the restriction requirement is withdrawn.

Claims 32-37, 40-41 are pending in the instant application and are currently under prosecution.

SEQUENCE RULE COMPLIANCE

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the following reasons:

1. The recited sequence in figure 3 legend is not accompanied by a sequence identification number.

OBJECTION

1. The specification is objected to because open space is found in the specification, e.g. on pages 2, 10.

2. The recitation of "the related application" on page 2 of the specification is objected to, because the following application is missing: Application 09/751,798, which

is a divisional of the instant application, as recited in the application transmittal of 12/17/01.

It is suggested that Applicant corrects and updates "the related application" as follows:

This application is a divisional of Serial No. 09/751,798, filed December 29, 2000, now US patent No. 6,525,177, which is a continuation-in-part of Serial No. 08/937,263, filed September 15, 1997, now US patent No. 6,274,145, which is a continuation-in-part of serial No. 08/725,182, filed October 3, 1996 now U.S. Patent No. 5,804,381.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 32-37, 40-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32-37, 40-41 are rejected under 35 U.S.C. 112, second paragraph, because claim 32 is incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the hybridization solutions for hybridization at 65^0C for 18 hours.

REJECTION UNDER 35 USC 101, DOUBLE PATENTING

35 U.S.C. 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory

double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 32, 40 of the instant application are non-provisionallly rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claim 5 of US Application Serial No. 09/751,798, now US patent No. 6,525,177.

Claims 32, 40 of the instant application are drawn to an isolated protein consisting of an immunoreactive portion of the protein encoded by an isolated nucleic acid molecule, the complementary sequence of which hybridizes to the nucleic acid sequence of SEQ ID NO:1 at 65^0 C for 18 hours, followed by four one hour washes at 2xSSC, 0.1% SDS, and a final wash at 0.2xSSC. Said immunoreactive portion of the protein is an amino acid sequence of a tumor rejection antigen.

Claim 5 of US 6,524,177 is drawn to an isolated tumor rejection antigen precursor protein which is expressed by melanoma cells, wherein said tumor rejection antigen precursor protein which elicits a humoral response by a human against said tumor rejection antigen precursor protein is encoded by a cDNA molecule, the complementary sequence of which hybridizes to the cDNA molecule consisting of nucleotides 54-600 of SEQ ID NO: 1, at 65.degree.C., 2.times.SSC, 0.1% SDS, followed by a wash at 0.2.times.SSC, 0.1.times.SDS, for 30 minutes at 65.degree.C.

It is noted that since there is no definition of "immunoreactive portion" in the specification of the instant application, it is assumed for the purpose of compact prosecution that an immunoreactive portion could be include full length portion, i.e. full length protein.

The specification of the instant application discloses that SEQ ID NO:1 is expressed in melanoma cells (p.14-15), and melanoma patients have antibody response to the NY-ESO-1 protein encoded by SEQ ID NO:1 (p.15, first paragraph). In addition, SEQ ID NO:1 of the instant application is the same as SEQ ID NO:1 of US 6,524,177 (see sequence listing).

The immunoreactive portion of the protein claimed in the instant application seems to be the same as the tumor rejection precursor protein of US 6,524,177, and encoded by the same nucleic acid molecule, or cDNA molecule, for the following reasons:

One would have expected that the complementary sequence which hybridizes to the fragment of SEQ ID NO:1, consisting of nucleotides 54-600 of SEQ ID NO:1, under the hybridization and wash conditions recited in claim 5 of US 6,524,177 would also hybridize to SEQ ID NO:1 under the hybridization and wash conditions recited in claim 32 of the instant application . In other words, the encoding nucleic acid molecule of the instant application seems to be the same as the encoding cDNA molecule of claim 5 of US 6,524,177.

Further, one would have expected that the immunoreactive portion of the protein claimed in the instant application is expressed by melanoma cells, and elicits a humoral

response by a human against said protein, because the instant specification discloses that SEQ ID NO:1 is expressed in melanoma cells (p.14-15), and melanoma patients have antibody response to the NY-ESO-1 protein encoded by SEQ ID NO:1 (p.15, first paragraph). In other word, one would have expected that similar to the tumor rejection antigen precursor protein of claim 5 of US 6,524,177, the protein of the instant application expresses in melanoma cells, and elicits a humoral response in a human.

Although US 6,524,177 does not specifically teach an immunoreactive portion of the protein encoded by an isolated nucleic acid molecule, the complementary sequence of which hybridizes to the nucleic acid sequence of SEQ ID NO:1 at 65^0 C or 18 hours, followed by four one hour washes at 2xSSC, 0.1% SDS, and a final wash at 0.2xSSC, however, the claimed immunoreactive portion appears to be the same as the tumor rejection antigen precursor protein of US 6,524,177, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of US 6,524,177 does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Thus, although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept.

This is a non-provisional obviousness-type double patenting rejection because the conflicting claims have in fact been patented.

2. Claims 36, 37 of the instant application are non-provisionallly rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claim 5 of US Application Serial No. 09/751,798, now US patent No. 6,525,177, in view of US 6, 274,145, and Roitt et al, eds,1996, Immunology, 4th ed, Mosby, London, p. 19.8-19.9.

Claims 36-37 of the instant application are drawn to a composition comprising an isolated protein consisting of an immunoreactive portion of the protein encoded by an isolated nucleic acid molecule, the complementary sequence of which hybridizes to the nucleic acid sequence of SEQ ID NO:1 at 65^0 C or 18 hours, followed by four one hour washes at 2xSSC, 0.1% SDS, and a final wash at 0.2xSSC, and an adjuvant, wherein said adjuvant is saponin, GM-CSF or an interleukin.

The teaching of claim 5 of US 6,525,177 has been set forth above.

Claim 5 does not teach a composition comprising an immunoreactive portion of the protein encoded by an isolated nucleic acid molecule, the complementary sequence of which hybridizes to the nucleic acid sequence of SEQ ID NO:1 at 65^0 C or 18 hours, followed by four one hour washes at 2xSSC, 0.1% SDS, and a final wash at 0.2xSSC, and an adjuvant, wherein said adjuvant is saponin, GM-CSF or an interleukin

US 6, 274,145 teach an immunogenic composition comprising a peptide and an adjuvant, wherein said adjuvant is saponin, GM-CSF or an interleukin (calims 3-4).

Roitt et al teach that adjuvants concentrate antigen to the site where lymphocytes are exposed to it, and directing the immune response in the desired direction (p. 19.8, second column, and p.19.9, first column, first paragraph). Roitt et al further teach that cytokines themselves have been shown be effective adjuvants, and may be particularly useful in immunocompromised patients (p. 19.8, second column, and p.19.9, first column, first paragraph).

It would have been obvious to add adjuvants such as saponin, GM-CSF or an interleukin, taught by US 6, 274,145, to a composition comprising the tumor rejection antigen precursor protein taught by claim 5 of US 6,525,177, because adjuvants concentrate antigen to the site where lymphocytes are exposed to it, and directing the immune response in the desired direction, and further may be particularly useful in immunocompromised patients, as taught by Roitt et al.

Thus, although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept.

This is a non-provisional obviousness-type double patenting rejection because the conflicting claims have in fact been patented.

3. Claims 32, 36-37, 40- 41 of the instant application is non-provisionallly rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claim 1 of US Application Serial No. 08/937,263, now US patent No. 6,274,145.

Claim 41 of the instant application are drawn to an isolated protein consisting of an immunoreactive portion of the protein encoded by an isolated nucleic acid molecule,

the complementary sequence of which hybridizes to the nucleic acid sequence of SEQ ID NO:1 at 65^0 C or 18 hours, followed by four one hour washes at 2xSSC, 0.1% SDS, and a final wash at 0.2xSSC, wherein said immunoreactive portion of the protein is an amino acid sequence of a tumor rejection antigen, and wherein said amino acid sequence is the amino acid sequence set forth in SEQ ID NO: 5 or 6.

Claim 1 of US 6,274,145 is drawn to an isolated peptide which binds to an HLA molecule, wherein the amino acid sequence of said peptide consists of SEQ ID NO: 5 or 6.

The specification of US 6,274,145 teaches screening of peptides of NY-ESO-1 protein (encoded by SEQ ID NO:1), and that peptide of SEQ ID NO:4-6 are the best stimulators of CTLs (Example 6, pages15-16, and Example 11, pages 21-22).

It is noted that the structure of SEQ ID NO: 1, 5 or 6 of US 6,274,145 is the same as SEQ ID NO:1, 5 or 6 of the instant application (see sequence listing)..

It is further noted that one would have expected that the complement of SEQ ID NO:1, which encodes the protein comprising SEQ ID NO:5 or 6 of US 6,274,145, would hybridize to SEQ ID NO:1 of the instant application, under the hybridization and wash conditions recited in claim 32 of the instant application.

The peptide consisting of SEQ ID NO:5, or 6 of claim 1 of US 6,274,145 seems to be the same as the claimed peptide of SEQ ID NO:5 or 6.

Although US 6,274,145 does not specifically teach that SEQ ID NO:5 or 6 is a portion of a protein encoded by an isolated nucleic acid molecule, the complementary sequence of which hybridizes to the nucleic acid sequence of SEQ ID NO:1 at 65^0 C or

18 hours, followed by four one hour washes at 2xSSC, 0.1% SDS, and a final wash at 0.2xSSC, wherein said immunoreactive portion of the protein is an amino acid sequence of a tumor rejection antigen, however, the claimed peptides appears to be the same as the peptides of US 6,274,145, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of US 6,274,145 does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Thus, Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept.

This is a non-provisional obviousness-type double patenting rejection because the conflicting claims have in fact been patented.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims **32-37, 40** are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims **32-37, 40** are drawn to an isolated protein consisting of an immunoreactive portion of the protein encoded by an isolated nucleic acid molecule, the "complementary" sequence of which "hybridizes" to the nucleic acid sequence of SEQ ID NO:1 at 65^0 C or 18 hours, followed by four one hour washes at 2xSSC, 0.1% SDS, and a final wash at 0.2xSSC. Said immunoreactive portion of the protein is an amino acid sequence of a tumor rejection antigen.

It is noted that in view of the lack of definition of "the complementary sequence" in the specification, the complementary sequence could be reasonably interpreted as a partial or full length complement, wherein a partial complement could share with the claimed nucleic acid molecule encoding a fragment of a tumor rejection antigen precursor or a tumor rejection antigen only a few nucleotides.

In addition, it is noted that hybridizing and wash under the hybridization and wash conditions as recited in claim 32 does not preclude hybridizing to only part of SEQ ID NO:1.

Thus, as written, the isolated nucleic acid encoding the claimed immunoreactive portion of claims 32-37 encompasses a nucleic acid molecule of any size and structure, wherein a complement of said nucleic acid molecule hybridizes to SEQ ID NO:1 via a common fragment, under the hybridization and wash conditions recited in claim 32.

In addition, it is noted that there is no definition of a tumor rejection antigen in the specification and in claim 40, which encompasses any tumor antigen.

Thus, the isolated nucleic acid encoding the claimed immunoreactive portion of claim 40 encompasses a nucleic acid molecule of any size and structure, provided it is from a tumor, wherein a complement of said nucleic acid molecule hybridizes to SEQ ID NO:1 via a common fragment, under the hybridization and wash conditions recited in claim 32.

Thus the claims encompass portions of proteins encoded by numerous variants of the polynucleotide of SEQ ID NO:1, with unknown structure and function.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that [a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials. Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as vertebrate insulin cDNA or mammalian insulin cDNA without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in

> the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of the isolated nucleic acid molecule, per Lilly by structurally describing a representative number of the hybridizing polynucleotides or by describing structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe the isolated nucleic acid molecule required to practice the **claims 32-37, 40** in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any hybridizing polynucleotide, other than SEQ ID NO:1, nor does the specification provide any partial structure of such hybridizing polynucleotide, nor any physical or chemical characteristics of the hybridizing polynucleotide other than SEQ ID NO:1, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single polynucleotide, SEQ ID NO:1, this does not provide a description of the hybridizing polynucleotides that would satisfy the standard set out in Enzo.

The specification also fails to describe the hybridizing polynucleotide by the test set out in Lilly. The specification describes only a single polynucleotide, SEQ ID NO:1.

Therefore, it necessarily fails to describe a representative number of such species. In addition, the specification also does not describe structural features common to the members of the genus, which features constitute a substantial portion of the genus.

Thus, the specification does not provide an adequate written description of the hybridizing polynucleotide that is required to practice the claimed invention. Since the specification fails to adequately describe the hybridizing polynucleotides, it also fails to adequately describe the immunoreactive portions of the proteins encoded by said hybridizing polynucleotides.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Claims **32-37, 40** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated protein consisting of an immunoreactive portion of a protein encoded by the nucleotide sequence of SEQ ID NO:1, or the amino acid sequence consisting of SEQ ID NO: 4, 5 or 6, **does not reasonably provide enablement for** an isolated protein consisting of **an immunoreactive portion of the protein encoded by an isolated nucleic acid molecule, the "complementary" sequence of which "hybridizes" to the nucleic acid sequence of SEQ ID NO:1 at 65^0 C or 18 hours, followed by four one hour washes at 2xSSC, 0.1% SDS, and a final wash at 0.2xSSC, wherein said immunoreactive portion of the protein is an amino acid sequence of a tumor rejection antigen**. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims **32-37, 40** are drawn to an isolated protein consisting of an immunoreactive portion of the protein encoded by an isolated nucleic acid molecule, the "complementary" sequence of which "hybridizes" to the nucleic acid sequence of SEQ ID NO:1 at 65^0 C or 18 hours, followed by four one hour washes at 2xSSC, 0.1% SDS, and a final wash at 0.2xSSC. Said immunoreactive portion of the protein is an amino acid sequence of a tumor rejection antigen.

It is noted that in view of the lack of definition of "the complementary sequence" in the specification, the complementary sequence could be reasonably interpreted as a partial or full length complement, wherein a partial complement could share with the claimed nucleic acid molecule encoding a fragment of a tumor rejection antigen precursor or a tumor rejection antigen only a few nucleotides.

In addition, it is noted that hybridizing and wash under the hybridization and wash conditions as recited in claim 32 does not preclude hybridizing to only part of SEQ ID NO:1.

Thus, as written, the isolated nucleic acid encoding the claimed immunoreactive portion of claims 32-37 encompasses a nucleic acid molecule of any size and structure, wherein a complement of said nucleic acid molecule hybridizes to SEQ ID NO:1 via a common fragment, under the hybridization and wash conditions recited in claim 32.

In addition, it is noted that there is no definition of a tumor rejection antigen in the specification and in claim 40, which encompasses any tumor antigen.

Thus, the isolated nucleic acid encoding the claimed immunoreactive portion of claim 40 encompasses a nucleic acid molecule of any size and structure, provided it is from a tumor, wherein a complement of said nucleic acid molecule hybridizes to SEQ ID NO:1 via a common fragment, under the hybridization and wash conditions recited in claim 32.

Thus the claims encompass portions of proteins encoded by numerous variants of the polynucleotide of SEQ ID NO:1, with unknown structure and function.

Applicants have not shown how to make and use the claimed immunoreactive portions of the proteins encoded by variants of SEQ ID NO:1, which are capable of functioning or have the properties of SEQ ID NO:1.

One cannot extrapolate the teaching in the specification to the scope of the claims because one cannot predict that the polypeptide sequences encoded by the variants of the polynucleotide of SEQ ID NO:1 would have properties related to that of SEQ ID NO:1. It is well known in the art that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein, and that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted

structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

Further, one cannot predict whether the polypeptides encoded by the variants of SEQ ID NO:1 would contain any peptide fragments that could elicit a T cell response, such as binding to MHC molecule, leading to recognition by CTLs specific for the polypeptide encoded by SEQ ID NO:1. As written, the claimed variant polypeptides

could be different from the polypeptide encoded by SEQ ID NO:1 at any amino acid position, throughout the whole length of the polypeptide, and one cannot predict that said difference would not destroy the property of being recognized by CTLs specific for the polypeptide encoded by SEQ ID NO:1. It is well known in the art that not any peptide would be recognized by the MHC molecules, and that certain characteristic motifs comprising certain specific amino acids at certain positions of a peptide that binds to a MHC molecule are required for fitting into the groove of the MHC molecule, and could not be replaced with different amino acids. The T cell receptor (TCR) complex recognizes a specific peptide lodged in the peptide binding groove of the MHC moleculel. This interaction dictates immunospecificity, since a peptide associated with an MHC molecule of one particular haplotype forms a unique structure to be recognized by the TCR (Roitt et al, eds,1996, Immunology, 4th ed, Mosby, London, p.7.8-7.10 and figures 7.22, 7.23, p. 8.1, first column, first six lines of second paragraph). Similarly, Stites DP et al, eds, 1997, Medical Immunology, 9th ed, Appleton & Lange, Stamford, Connecticut, pages 90-91, teach that T cell receptors (TCRs) recognize peptide-MHC complexes by binding simultaneously to specific residues both in the peptide and in the highly polymorphic region of the MHC molecule in and around the peptide-binding groove, and that as a result, individual TCRs are capable of discriminating not only among peptides but also among different allelic forms of a given MHC protein (p.90, second column, last paragraph, bridging p.91). Thus in view of the teaching in the art and in the specification, one cannot predict that the claimed immunoreactive portions

would have the property of being recognized by CTLs specific for the polypeptide encoded by SEQ ID NO:1 .

The specification does not disclose how to make the protein, and the claimed immunoreactive portion thereof, encoded by the variant nucleic acid molecules, such that they would function as the protein and immunoreactive portion thereof, encoded by the polynucleotide of SEQ ID NO:1, or have the properties such as being recognized by CTLs specific for the polypeptide encoded by SEQ ID NO:1, or how to use said immunoreactive portion if they did not have the function or properties claimed.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

2. If Applicant could overcome the above 112, first paragraph, Claims **33-35 are still** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the full length amino acid sequence encoded by SEQ ID NO: 1, wherein said amino acid sequence is processed by a cell to form a peptide which complexes to an MHC molecule and is recognized by specific CTLs **does not reasonably provide enablement for "an immunoreactive portion" of the protein** encoded by an isolated nucleic acid molecule, the complementary sequence of which hybridizes to the nucleic acid sequence of SEQ ID NO:1 at 65^0 C or 18 hours, followed by four one hour washes at 2xSSC, 0.1% SDS, and a final wash at 0.2xSSC, **wherein said immunoreactive portion of the protein is processed by a cell to form a peptide which complexes to an MHC molecule and provides "a T cell response".** The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims **33-35** are drawn to an isolated protein consisting of an immunoreactive portion of the protein encoded by an isolated nucleic acid molecule, the complementary sequence of which hybridizes to the nucleic acid sequence of SEQ ID NO:1 at 65^0 C or 18 hours, followed by four one hour washes at 2xSSC, 0.1% SDS, and a final wash at 0.2xSSC, wherein said immunoreactive portion of the protein is processed by a cell to form a peptide which complexes to an MHC molecule and provides a T cell response. Said MHC molecule is a Class I or Class II molecule.

The specification discloses that the polynucleotide of SEQ ID NO:1 (NY-ESO-1) is expressed in patients with melanoma, ovarian cancer, breast cancer and lung cancer, and in normal uterus, testis and ovary (Tables 2-4 on pages 12-13). The specification further discloses that melanoma patients contain antibodies to SEQ ID NO:1 in serum (p.15, first paragraph).

The specification discloses that specific CTLs lyse both the NW38 MEL tumor cell line and the cell lines that are ESO-1 (i.e. full length sequence of SEQ ID NO:1) positive (Example 10 on pages 22-23 and figure 6).

The specification also discloses that the peptides of SEQ ID NO:4, 5 and 6 are the three best stimulators of CTLs, using the autologuous NW38 MEL tumor cell line and the allogeneic cell lines that are ESO-1 (i.e. full length sequence of SEQ ID NO:1) positive as targets (Example 12, on pages 24-25).

The specification further discloses identification of several peptides from SEQ ID NO:1 that have HLA binding motifs and expects that said peptides bind to HLA and provoke a cytolytic T cell response (Example 13 on pages 25-26).

The specification contemplates administrating to a patient having tumors peptides of the protein encoded by SEQ ID NO:1, that bind to the MHC/HLA molecules and provoke lysis of target cells by T cells (p.29, from lines 16 to the end of p.29).

No disclosure is found concerning in vivo example of induction of T cell response in cancer patients by the full length SEQ ID NO:1, or the peptides of SEQ ID NO: 4, 5, or 6.

1. Claims 33-35 encompasses "any immunoreactive portion" of a protein encoded by SEQ ID NO:1, wherein said portion could be processed by a cell to form a peptide which complexes to an MHC molecule and provides "any T cell response".

One cannot extrapolate the teaching in the specification to the scope of the claims, because although the specification identifies several peptides that potentially could bind to HLA, it is well known in the art that not any peptide that potentially binds to HLA would induce T cell response. For example, Kirkin et al, 1998, APMIS, 106 : 665-679 teach that for the melanocyte differentiation antigen Melan-A/MART-1, some Melan-A/MART-1 peptides although having high affinity of HLA-A2.1 antigen do not induce the generation of melanoma-specific CTL in vitro, from PBL of melanoma patients (p.670, first column, last paragraph, bridging second column). Kirkin et al further teach that so far only two peptides have been identified, one of which, peptide

27-35, is shown to be recognized by TIL cultures reacting against Melan-A/MART-1 and to induce generation of melanoma-specific CTL in vitro from PBL of melanoma patients. Moreover, as shown in table 1, on page 667 in the reference by Kirkin et al, for each melanoma associated antigen, only a few peptides have been identified as being recognized by CTLs, most of which however have low immunogenecity (Kirkin et al, p.673, first column, paragraph under immunogenecitiy of tumor cells). Thus one cannot predict that any fragment or any portion of the protein encoded by SEQ ID NO:1 would elicit a T cell response.

In addition, although claim 41, reciting SEQ ID NO:4-6, does not depend on claim 33, claim 41 reads on claim 33, in view that the specification discloses that the peptides of SEQ ID NO:4-6 are strong stimulators of CTLs specific for the polypeptide encoded by SEQ ID NO:1. However it is not clear on what basis that statement in the specification was made, especially in view of the above teaching of Kirkin et al that only few peptides from melanoma associated antigens have been so far identified as being recognized by specific CTLs, and it is unpredictable that not any peptides would be recognized by CTLs. Thus, in view of the lack of objective evidence, and further in view of the above teaching by Kirkin et al, one cannot assess that these peptides of SEQ ID NO:4-6 have specific sequences that are recognized by specific T cell receptors, and thus it cannot be extrapolated that any peptide sequences from the polypeptide encoded by SEQ ID NO:1 would elicit a T cell response, because it is unpredictable that any peptide sequences would bind to HLA and induce a specific T cell response, for reasons set forth above, and in view of the teaching of Kirkin et al, supra.

Further, the claims encompass an immunoreactive portion that provides any T cell response such as activation of suppressor T cells, which suppresses the immune response (Roitt et al, eds,1996, supra, p.2.6, first column, second paragraph). It is noted however that activation of suppressor T cells would be a T cell response opposite to induction of lysis by specific CTLs. Since one cannot predict that the claimed any immunoreactive portion could activate a T cell response, one cannot predict either that the claimed immunoreactive portion is capable of activate any T cell response, such as T cell suppressor.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability that any fragment or any portion of the protein encoded by SEQ ID NO:1 would elicit any T cell response, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is

known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

2. Further, as written, the claims 33-35 encompass **an immunoreactive portion of a protein encoded by SEQ ID NO:1, wherein said portion** could be processed by a cell to form a peptide which complexes to an MHC molecule and **provides a T cell response "in vivo" in cancer patients, as contemplated.**

One cannot extrapolate the teaching in the specification to the scope of the claims, because it is unpredictable that in vivo, the claimed immunoreactive portion of the protein encoded by SEQ ID NO:1 would provide an adequate T cell response, useful for immunotherapy, as contemplated. The *in vitro* demonstration of CTLs stimulated lysis of tumor cells lines by the polypeptide encoded by SEQ ID NO:1, or in vitro CTLs stimulation by SEQ ID NO:4, 5 or 6, cannot be correlated to the invention as contemplated, because the CTLs are continuously in contact with target cells in *in vitro* assays and are not subjected to the defense of the body. Further, Kirkin et al, 1998, APMIS, 106 : 665-679, review several melanoma-associated antigens, including NY-ESO1, and conclude that initiation of a strong immune response in vivo is an extremely rare event (p.674, first column, last paragraph). Kirkin et al teach that for some antigens, due to the existence of self-tolerance, only T cells with low affinity T-cell receptors are produced (abstract). Kirkin et al teach that although several peptides of melanoma associated antigens have been identified as recognized by CTL in vitro, and peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response in vivo, only one of the peptides, peptide EVDPIGHLY of

MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity (p.666, second column, second paragraph, last 6 lines). Further, even this peptide EVDPIGHLY of MAGE-A3 produces a very low level of CTL response which is detectable only by a very sensitive method, as taught by Chaux et al, Int J Cancer, 1998, 77: 538-542, abstract. Chaux et al further teach some of the CTLs have an affinity that is too low for the recognition of cells that have processed the antigen, which is different from the in vitro conditions in which the synthetic peptides are in high number when incubated with the cells (p.541, second column, second paragraph). Similarly Sherman, LA et al, 1998, Critical reviews in Immunol, 18(1-2): 47-54 teach that self-tolerance may eliminate T cells that are capable of recognizing these epitopes with high avidity . In other words, only CTLs with low affinity are left, which may not be effective for tumor treatment *in vivo*. Smith RT, 1994, Clin Immunol, 41(4): 841-849, teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limits the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specfic antigen in the necessary MHC context (p.484).

Thus based on the teaching in the art and in the specification, one cannot predict that an adequate in vivo T cell response useful for immunotherapy, as contemplated,

could be induced by the claimed immunoreactive portions of a protein encoded by SEQ ID NO:1 in patients having tumor burden.

Given the unpredictability that any fragment or any portion of the protein encoded by SEQ ID NO:1 would elicit an adequate T cell response in vivo, useful for immunotherapy, as contemplated, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, YVONNE EYLER can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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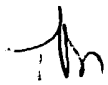

MINH TAM DAVIS

PATENT EXAMINER

February 13, 2004